UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,028	08/16/2001	Takami Maekawa	212833US0PCT	1278

22850 7590 03/25/2003

OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,028	MAEKAWA ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☒ Claim(s) *4-8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11/16/01; 12/3/01; 10/17/02
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Acknowledgement of claim to foreign priority of Japanese Application, 11/38538, filed 2/17/1999 under 35 U.S.C. 119(a)-(d) has been made, however applicant should note that the certified copy and translation of this foreign priority document has not yet been received and as a result the claim to foreign priority under the same has not yet been granted.

Claim Objections

1. Claims 4-8 are objected to under 37 CFR 1.75(c) as being in improper form because the multiple dependent claim 4 depends from the multiple dependent claim 3. See MPEP § 608.01(n). Accordingly, the claims 4-8 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 is indefinite over the recitation of "inner position." It is unclear if the applicant intended for inner position to be "inner" as compared to the newly synthesized cDNA, or alternatively "inner" as meaning away from the end of the vector, in which case "inner" would be on the opposite side of "inner" using the cDNA as a reference point. Applicant should amend

the claim to clarify their intended meaning and placement of the restriction enzyme site that is placed in an "inner" position. Applicant should also note that this method requires specific direction to the exact location of elements. Applicant should amend the claims to state explicitly where the restriction enzyme sites are located, oligonucleotides anneal, etc. as precision of element location is critical to applicant's invention.

B. Claim 1 is further indefinite over the recitation of "near the other end." The reference point for this phrase is the "inner" position which is indefinite as seen above, and as a result its use as a reference point makes further positions indefinite. It is unclear if "other end" is at the most 3' portion of the newly synthesized cDNA or alternatively(using the other meaning of "inner") is located at the opposite end of the now linearized vector. Applicant should amend the claim to clarify their intended meaning and placement of the restriction enzyme site that is placed "near the other end" of the, "inner" position.

C. Claim 1 is further indefinite over the recitation of "oligonucleotides having nucleotide sequences corresponding to respective flanking regions of the both sides of the tag." It is unclear how sequences of the vector will necessarily still be present at this point in the method, following the instructed restriction digestions. As the points at which restriction digestion are indefinite, it is not possible to assume that vector sequences characteristic to only **some** permutations of possible restriction digestions, would necessarily be always present. Applicant should amend the claims to clarify the oligonucleotides to be used in tag amplification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler et al. in view of Okubo et al. (DNA Sequence, 1991).

Kinzler et al. teach a method for analyzing expression frequencies of genes, which comprises the following steps:

(a) a step of forming a vector primer to which each mRNA derived from a cell of which expression frequencies of genes is to be analyzed, and synthesizing the cDNA, said vector primer comprising a capture system to isolate the defined 3' nucleotide sequence tag when the oligo dT primer for biosynthesis is present(US5,695,937 Col. 5 and Col.6 lines 43-57), along with a recognition sequence for a first restriction enzyme in an inner position from the poly(T) sequence(See FIG.1A and Col.5 lines 4-25), a recognition sequence for a second restriction enzyme near the other end, and a recognition sequence for a type IIS restriction enzyme in an inner position from the recognition sequence for the second restriction enzyme(See FIG. 1A and Col. 5 lines 12-27 and lines 50-60). The reference is generally teaching the purposeful step of

focusing only on the 3' sequences(via combination of capture mechanism and selective restriction digestion) of any gene to maximally identify genes through matching ESTs.

(b) a step of digesting the vector primer to which the cDNA is ligated, with the second restriction enzyme and a third restriction enzyme that does not digest the vector primer as the reference teaches that the invention is not limited to the use of a single first restriction endonuclease or second as "it may be desirable to perform the method of the invention sequentially, using different enzymes to identify a complete pattern of transcription(Col. 5 lines 12-27). The reference further teaches cleaving with restriction enzymes to create compatible, "same shape" ends and "procedures for cloning the defined nucleotide sequence tags of the invention is insertion of the tags into vectors such as plasmids or phage"(Col.7, lines 5-43).

(c) a step of digesting the cyclized vector primer with the first restriction enzyme and the type IIS restriction enzyme to excise a downstream region of the cDNA so that a tag consisting of a part of the cDNA is left, and cyclizing the vector primer again is taught in the reference's Example 1, as they teach that following restriction digestion, the "ditag products were cleaved with NlaIII and...were cloned into the SphI site of pSL301"(Col. 9, lines 10-60).

(d) a step of performing polymerase chain reaction (PCR) by using the vector primer as a template and oligonucleotides having nucleotide sequences corresponding to respective flanking regions of the both sides of the tag contained in the vector primer as primers to amplify the tag, was taught in the reference as "the ditag can be amplified by utilizing primers which specifically hybridize...and using the standard polymerase chain reaction(PCR) or alternatively by cloning in prokaryotic-compatible vectors"(Col.6, lines 36-57). The reference goes on to teach that "primers are selected to be substantially complementary to the different strands of each specific

sequence to be amplified, and that the primers must be sufficiently long to prime the synthesis of extension products in the presence of the agent for polymerization.

(e) a step of ligating the amplification products to form a concatemer of the tags as the reference teaches "preferably, the ditags or concatemers thereof are ligated into a vector for sequencing purposes"(Col.7 lines 23-43).

(f) a step of determining the nucleotide sequence of the concatemer and investigating types and frequencies of tags occurring in the nucleotide sequence.(Col.7 lines 23-43) The reference is generally teaching the concept that through sequencing only a few nucleotide bases for each template it is possible to index the expressed gene in a much smaller scale and thereby affording the ability to identify differentially expressed genes genome wide.

The reference further teaches the above method wherein the ligation reaction in the step (e) is performed in the presence of an adaptor having one end of the same shape as an end of the tag to arrange the adaptor at each end of the concatemer, and the concatemer is amplified by performing PCR using oligonucleotide having a sequence corresponding to the sequence of the adaptor as a primer(See FIG.1A and FIG.1B).

Kinzler et al. does not teach in step (a) a vector primer comprising a linear plasmid vector having a single-stranded poly(T) sequence at one 3' end a recognition sequence for a second restriction enzyme near the other end, and a recognition sequence for a second restriction enzyme near the other end, and a recognition sequence for a type IIS restriction enzyme in an inner position from the recognition sequence for the second restriction enzyme, nor does the reference teach a step of digesting the vector primer to which the cDNA is ligated, with the second restriction enzyme and a third restriction enzyme that does not digest the vector primer

and forms a digested end of the same shape as a digested end obtained with the second restriction enzyme, to excise an upstream region of the cDNA, and cyclizing the vector primer.

However, Okubo et al teach step (a) a vector primer comprising a linear plasmid vector having a single-stranded poly(T) sequence at one 3' end a recognition sequence for a second restriction enzyme near the other end, and a recognition sequence for a second restriction enzyme near the other end, and a recognition sequence for a type IIS restriction enzyme in an inner position from the recognition sequence for the second restriction enzyme, and also Okubo et al. teaches a step of digesting the vector primer to which the cDNA is ligated, with the second restriction enzyme and a third restriction enzyme that does not digest the vector primer and forms a digested end of the same shape as a digested end obtained with the second restriction enzyme, to excise an upstream region of the cDNA, and cyclizing the vector primer(Pg. 138 figures a-d). Okubo et al. teach a method for constructing a library containing the 3' end fragment of cDNA for large scale sequencing of cDNA clones. The reference teaches using a T-tailed vector primer for first strand synthesis, "because it is the most efficient way to prepare the cDNA molecule for directional cloning"(Pg. 137). Okubo teach that the vector plasmid was pUC19 that has the M13 sequence flanking the cloning site. The presence of this flanking sequence, is taught by the reference to allow for common primers to be used for PCR amplification of insert cDNAs as well as for their subsequent sequencing. The reference further teaches the second strand synthesis to be initiated by nick translation and the resulting molecule to be digested with *MboI* and *BamHI*. *MboI* is used as it will cut within a few hundred bases away from the poly A tail. The reference continues to teach that *BamHI*, whose recognition sequence includes that of *MboI*, makes cohesive termini at the other end of the vector DNA, and

therefore, the resulting cleavage products could be circularized in a diluted condition with *E. coli* ligase which cannot ligate unreacted vector primers or undigested molecules(Pgs 137 and 138).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the first principle of the Kinzler method, creating a short nucleotide sequence tag and anchoring it to a streptavidin bead so as to have instead included a method wherein the 3'end fragments of genes are instead anchored to a vector by way of the vector primer methodology taught by Okubo et al. since the method of Okubo provided a "high efficiency that was considered to have been due to the simplicity of the protocol"(Pg 138). Kinzler et al. in its entirety teaches a method "consisting of the same three major principles that define the present application: First, a short nucleotide sequence tag (ex. 9 to 10bp) contains sufficient information content to uniquely identify a transcript provided it is isolated from a defined position within the transcript. Second, random dimerization of tags allows a procedure for reducing bias (caused by amplification and or cloning). Third, concatenation of these short sequence tags allows the efficient analysis of transcripts in a serial manner by sequencing multiple tags within a single vector or clone"(Col.3 lines 25-50). The reference also teaches "all of these principles may be applied independently, in combination, or in combination with other known methods of sequence identification"(Col.3 lines 25-50). To put it even more simply, the reference teaches a method in which very short (9-14 bp) cDNA tags are generated by restriction digestion, amplified by PCR and ligated, after which the resulting concatemers are sequenced. The tags of the reference and present invention are long enough to identify the corresponding genes unequivocally and the frequency of the tags is a measure of their expression level. As a result, since the method of Okubo presents just another way of capturing the 3' end of a gene

whose "high efficiency was considered to have been due to the simplicity of the protocol"(Pg 138); in comparison to the method taught by Kinzler, combining the teachings of Kinzler et al. in view of Okubo et al. would have been obvious at the time the invention was made.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

3/21/2003

JEFFREY FREDMAN
PRIMARY EXAMINER